EXHIBIT 5

Risk Factors for Pouch Failure in Patients with Different Phenotypes of Crohn's Disease of the Pouch

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Background: Crohn's disease (CD) of the pouch is one of the leading causes of pouch failure in patients with restorative proctocolectomy. Risk factors for pouch failure in these patients are yet to be identified. The aim of the study was to assess risk factors associated with pouch failure in patients with CD of the pouch.

Methods: All patients with a confirmed diagnosis of CD of the pouch in the Pouchitis Clinic between 2002 and 2007 were evaluated. Patients with familial adenomatous polyposis, normal pouches, pouchitis, cuffitis, surgical complications, and other diseased pouch conditions were excluded. Pouch failure was defined as the requirement for a permanent diversion or pouch resection. Demographic and clinical factors were studied with univariable and multivariable analyses.

Results: A total of 137 patients with CD of the pouch were included. Twenty-two patients (16%) developed pouch failure a median of 6 years after ileostomy takedown. Four of 50 patients (8.0%) with inflammatory CD, 4 of 30 (13.3%) with fibrostenotic CD, and 14 of 57 (24.6%) with fistulizing CD had pouch failure. A Kaplan-Meier plot for time to pouch failure by CD phenotype showed a trend toward association ($P = 0.054$) in patients with fistulizing CD. Adjusting for age, smoking status, and the use of immunomodulators or biologics, fistulizing CD was not found to be significantly associated with a higher hazard for pouch failure. Younger age, being an ex-smoker, and the use of immunomodulators or biologics were found to increase the hazard of pouch failure.

Conclusions: Younger age, being an ex-smoker, and the requirement for immunomodulators or biologics were associated with pouch failure. The identification of these risk factors may help delineate the natural history of CD of the pouch and shed light on proper clinical management and prognosis.

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Approximately 30% of patients with ulcerative colitis (UC) eventually require total proctocolectomy.[1] Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice for most UC patients with medically refractory disease or dysplasia, as well as for most patients with familial adenomatous polyposis (FAP).[2,3] The IPAA procedure is generally contraindicated in patients with a known diagnosis of Crohn's disease (CD) or Crohn's colitis before colectomy. Nonetheless, de novo CD can develop after IPAA in patients with a preoperative diagnosis of UC or indeterminate colitis (IC). CD of the pouch can be categorized into 3 clinical phenotypes: inflammatory, fibrostenotic, and fistulizing CD.[4] Prevalence of CD of the pouch ranged from 2.7% to 13%.[5–12] Pathogenesis and natural history of post-IPAA CD are yet to be investigated. Reported risk factors for CD of the pouch were long duration of having a pouch, being an active smoker,[13] a preoperative diagnosis of IC,[14] seroposistive anti-*Saccharomyces cerevisiae* IgA,[15] and a family history of CD.[13] Each of the clinical phenotypes of CD of the pouch was shown to be associated with different risk factors.[4]

CD of the pouch adversely affects outcomes and patients' health-related quality of life[16,17] and can lead to septic complications or pouch failure.[18,19] In fact, CD of the pouch is one of the leading causes of pouch failure, resulting in pouch resection or permanent diversion. Reported rates of pouch failure from CD ranged from 25% to 100%, depending on the duration and intensity of follow-up, the use of medical or endoscopic therapy, and the threshold of initiating the pouch resection operation.[2,6–12,20] Most of these reports, however, had come before the era of routine use of immunomodulators and biological therapy in CD. Long-term outcome for CD of the pouch needs to be investigated. Risk factors for pouch failure in these patients have not been studied. We hypothesized that certain demographic and clinical factors may predispose the patients to develop a refractory disease course, leading to pouch failure. The aim of the study was to evaluate the factors associated with pouch failure in these patients.

PATIENTS AND METHODS

Patients

The Cleveland Clinic Institutional Review Board approved this historical cohort study, and informed consent was obtained from all patients. A total of 602 patients were seen in our Pouchitis Clinic, staffed by an inflammatory bowel disease (IBD) specialist (B.S.) and 3 colorectal surgeons (V.W.F., F.H.R., I.C.L.), from March 2002 to November 2007.

Diagnostic Criteria

Patients with CD of the pouch were diagnosed based on a combined assessment of symptoms, endoscopy, histology, and radiography using the criteria previously published by our group.[4] CD of the pouch was categorized into 1 of 3 clinical phenotypes modified from the Vienna Classification[21] and the Montreal Classification:[22] inflammatory, fibrostenotic, and fistulizing CD.[23] *Inflammatory CD of the pouch* was defined as ulcerated lesions of the small bowel or afferent limb without diffuse pouchitis (excluding backwash ileitis from pouchitis) that persisted despite at least 4 weeks of antibiotic therapy. *Fibrostenotic CD of the pouch* was defined as the presence of ulcerated strictures in the small bowel, distal ileum, afferent limb, midpouch, or pouch inlet with concurrent ulcers or inflammation of the afferent limb. The diagnosis of inflammatory or fibrostenotic CD of the pouch was made after the exclusion of regular nonsteroidal anti-inflammatory drug use at the time of diagnosis.[24] *Fistulizing CD of the pouch* was defined as having a fistula that developed 12 months after the ileostomy takedown in the absence of surgically related local complications such as abscess, leak, anastomotic separation, sinus, and pelvic sepsis. The lesions included perianal fistulae, pouch-vaginal fistulae, pouch-bladder fistulae, enterocutaneous fistulae, or pouch cutaneous fistulae.

Inclusion and Exclusion Criteria

To qualify for the study, patients with CD of the pouch needed to meet all the following inclusion criteria: (1) >15 years old, (2) able to give consent, (3) undergoing evaluation and being regularly followed up in the Pouchitis Clinic, and having a diagnosis of CD of the pouch.[25] Exclusion criteria were: (1) having IPAA for FAP or colon neoplasm, (2) having healthy pouches, irritable pouch syndrome, pouchitis, and cuffitis; and (3) having local complications associated with surgery, such as pelvic sepsis, pelvic abscess, and pouch sinus.

Protocol

IPAA patients who met inclusion criteria and did not meet exclusion criteria were evaluated with a standard protocol. An outpatient evaluation with a combined assessment of demographic, clinical, endoscopic, and histologic features was conducted. All patients underwent outpatient pouch endoscopy with biopsy. Segmental evaluation and biopsy of the afferent limb, pouch, and rectal columnar cuff were performed during pouch endoscopy. The endoscopic features of each segment were documented, and biopsies were separately labeled and submitted. Examination under general anesthesia, retrograde contrasted pouchography, CT enterography, MRI of the pelvis, or small bowel capsule endoscopy was performed if the diagnosis of CD of the pouch was not conclusive by routine clinical, endoscopic, and histologic examination. Routine laboratory tests were performed for patients with persistent symptoms despite medical (with or with endoscopic) therapy, including complete blood cell counts, complete metabolic panel, blood cytomegalovirus DNA, celiac disease serology (total IgA, IgG and IgA antigliadin, and IgG and IgA antitissue transglutaminase), and stool for *Clostridium difficile* toxins A and B. All patients were followed for a minimum of 12 months after IPAA completion and the ileostomy closure.

Definitions of Variables

Demographic and clinical variables were defined as follows: smoking—consumption of more than 7 cigarettes per week for at least 6 months prior to the data entry; ex-smoker—cessation of smoking 6 months prior to data entry; duration of pouch—time interval between completion of IPAA with the ileostomy closure and data entry; duration of IBD—time interval between IBD diagnosis (i.e., preoperative diagnosis of UC, IC, or CD) and data entry; pancolitis—endoscopic, macroscopic, or microscopic disease extending proximal to the splenic flexure; indication for proctocolectomy and IPAA—primary reason for the surgery based on clinical presentation and preoperative diagnostic studies; toxic megacolon—presence of characteristic clinical and radiographic features together giving a clinical presentation of severe colitis; indeterminate colitis—histopathological diagnosis on proctocolectomy specimens that defied a clear distinction between CD and UC; Crohn's colitis—colitis with granulomas in the absence of related perianal, small bowel, and upper gastrointestinal lesions; preoperative use of biologics—any precolectomy use infliximab or adalimumab for IBD or concurrent autoimmune disorders, if present; use of topical or oral 5-aminosalicylates (5-ASA) or corticosteroids—use of topical or oral 5-ASAs or corticosteroids for a total of more than 6 months after ileostomy takedown; long-term use of antibiotics—use of oral ciprofloxacin, metronidazole, rifaximin, or tinidazole for more than 6 months per year after ileostomy takedown; use of immunomodulators—any use of immunomodulators for more than 6 months after ileostomy takedown for CD of the pouch, concurrent autoimmune disorders, or post–liver transplantation immunosuppression; post-IPAA use of biologics—any use of infliximab or adali-

mumab for CD of the pouch or concurrent autoimmune disorders, if present; long-term seton placement—seton in place for more than 12 months as a part of treatment of CD-related fistula or abscess after ileostomy takedown; incision and drainage—drainage procedure undertaken for CD-related abscess after ileostomy takedown; endoscopic dilation of stricture—through-the-scope balloon dilations of CD-related strictures during pouch endoscopy, with or without injection of long-acting corticosteroids; pouch failure—dysfunctional pouch requiring in-pouch resection or a permanent diversion; hospitalization—admission to our institution for at least 24 hours with a primary diagnosis related to disorder(s) of the pouch; and extraintestinal manifestations—including the presence of arthralgia or arthropathy, pyoderma gangrenosum, erythema nodosum, IBD-related ocular lesions, thromboembolic events, and primary sclerosing cholangitis.

Outcome Measurement

The primary outcome was assessment of the association between demographic and clinical factors and pouch failure.

Statistical Analysis

Descriptive statistics were computed for all factors. These include medians and percentiles for continuous factors and frequencies for categorical factors. Duration of the pouch was defined as the time from pouch creation to either pouch failure or as present if pouch had survived. A Kaplan-Meier plot was used for graphical representation of pouch-survival probabilities by CD phenotype. Univariable and multivariable Cox proportional hazards models were used to assess the association between several demographic and clinical factors and pouch failure. The association between pouch failure and clinical phenotype was assessed while adjusting for age, duration of IBD, and use of immunomodulators or biologics, one factor at a time. A significance level of 0.05 was considered for all analyses. SAS version 9.1 software (SAS Institute, Cary, NC) and R 2.0.1 software (The R Foundation for Statistical Computing) were used to perform all analyses.

RESULTS

The practice pattern of the Pouchitis Clinic determined that most patients had a diseased condition of the pouch. Of the 602 patients seen at the Pouchitis Clinic during the study period, 137 (22.8%) carried a diagnosis of CD of the pouch: 95 patients had IPAA performed at our institution, and 42 had the surgery at outside institutions. Pouch failure developed in 16% (n = 22) of the patients, with a median follow-up of 2 years at the Pouchitis Clinic. There was no mortality in this group of patients during the follow-up period.

Table 1 presents the demographic and clinical characteristics of the 137 patients with CD of the pouch. Median time from ileostomy takedown to pouch failure was 6 years (interquartile range: 4, 14), whereas median duration of the pouch for those without failure was 10 years (interquartile range: 6, 14; P = 0.057). Four of 50 patients (8%) with inflammatory CD, 4 of 30 (13.3%) with fibrostenotic CD and 14 of 57 (24.6%) with fistulizing CD developed pouch failure. Sixty-two patients (45.1%) with CD of the pouch were on immunomodulators. Of the 22 patients with pouch failure, 17 (77.3%) were on immunomodulators, whereas 45 patients (39.1%) in the non–pouch failure group were on immunomodulators. Two patients (3.5%) developed 6-mercaptopurine-induced pancreatitis. Thirty-one patients (22.6%) were treated with biologics. Of the 22 patients with pouch failure, 13 (59.1%) were treated with biologics, and 18 (15.7%) in the non–pouch failure groups were on biologics. None of the patients on biologics developed severe adverse effects or lymphoma during the follow-up period.

Figure 1 presents a Kaplan-Meier plot for time-to-pouch failure by CD phenotype. A trend toward association was observed (P = 0.054), with subjects with fistulizing CD having a worse pouch survival. Because the plot suggested the association between phenotype and pouch failure might change over time, the significance of the interaction between phenotype and follow-up time was assessed; this was not found to be statistically significant (P = 0.37). Compared with those with inflammatory and fibrostenotic CD, patients with fistulizing CD had 2.8 times (95% confidence interval: 1.2, 6.6) the hazard for pouch failure (P = 0.023). There was no significant difference in the hazard for pouch failure between patients with inflammatory CD and those with fibrostenotic CD (P = 0.74) or between subjects with fistulizing CD and those with fibrostenotic CD (P = 0.12). In an unadjusted Cox model, younger age; shorter duration of IBD; use of 5-ASAs, immunomodulators, or biologics; and hospitalization for pouch conditions were found to significantly increase the hazard for pouch failure (Table 2).

Adjusting for age, smoking status, and the use of immunomodulators or biologics, fistulizing CD was not found to be significantly associated with a higher hazard for pouch failure. However, younger age, being an ex-smoker, and using immunomodulators or biologics were found to increase the hazard for pouch failure in patients with CD (Table 3).

DISCUSSION

CD of the pouch has been found to occur in the following settings: (1) in a selected group of "highly motivated" patients with a preoperative diagnosis of Crohn's colitis in whom IPAA was *intentionally* performed,[26] (2) *inadvertently* in colectomy specimens of patients with a preoperative diagnosis of UC or IC during perioperative or postoperative histopathological examination,[6–10,27] and (3) de novo CD of the pouch developing weeks or years after ileostomy takedown, and a review of the proctocolectomy specimens may show no evidence of CD.[8,9] In our clinical practice, patients with known Crohn's colitis were considered not eligible to

TABLE 1. Demographic and Clinical Characteristics

Factor	All (n = 137)	Failure (n = 22)	No Failure (n = 115)
Age	42.0 (32.0, 50.0)	29.5 (25.0, 36.0)	45.0 (35.0, 51.0)
Duration of IBD (years)	17.0 (9.0, 23.0)	10.5 (7.0, 17.0)	17.0 (10.0, 25.0)
Duration of Pouch (years)	10.0 (6.0, 14.0)	6.0 (4.0, 14.0)	10.0 (6.0, 14.0)
Duration of Follow-up (years)	2.0 (1.0, 3.0)	2.0 (1.5, 3.0)	2.0 (1.0, 3.0)
Sex (female)	71 (51.8)	10 (45.5)	61 (53.0)
Race (white)	134 (97.8)	21 (95.5)	113 (98.3)
Ex-smoker	27 (19.7)	6 (27.3)	21 (18.3)
Current smoker	17 (12.4)	3 (13.6)	14 (12.2)
Clinical phenotype			
Inflammatory	50 (36.5)	4 (18.2)	46 (40.0)
Fibrostenotic	30 (21.9)	4 (18.2)	26 (22.6)
Fistulizing	57 (41.6)	14 (63.6)	43 (37.4)
J Pouch	124 (90.5)	20 (90.9)	104 (90.4)
Stage of pouch surgery			
1	7 (5.1)	0 (0.0)	7 (6.1)
2	105 (76.6)	16 (72.7)	89 (77.4)
3	19 (13.9)	6 (27.3)	13 (11.3)
4 or pouch redo	6 (4.4)	0 (0.0)	6 (5.2)
Indication for colectomy			
Refractory	123 (89.8)	22 (100.0)	101 (87.8)
Dysplasia	14 (10.2)	0 (0.0)	14 (12.2)
Panulcerative colitis	132 (96.4)	22 (100.0)	110 (95.7)
Toxic megacolon	10 (7.3)	2 (9.1)	8 (7.0)
Preoperative diagnosis			
Ulcerative colitis	119 (86.9)	20 (90.9)	99 (86.1)
Indeterminate colitis	14 (10.2)	2 (9.1)	12 (10.4)
Crohn's disease	4 (2.9)	0 (0.0)	4 (3.5)
Preoperative biological therapy	5 (3.7)	1 (4.6)	4 (3.5)
Post-IPAA topical 5-ASA	33 (24.6)	8 (36.4)	25 (22.3)
Post-IPAA oral 5-ASA	68 (50.8)	10 (45.5)	58 (51.8)
Post-IPAA topical corticosteroids	6 (4.5)	2 (9.1)	4 (3.6)
Post-IPAA oral corticosteroids	33 (24.6)	2 (9.1)	31 (27.7)
Long-term antibiotics	102 (76.1)	20 (90.9)	82 (73.2)
Immunomodulators after IPAA	62 (45.3)	17 (77.3)	45 (39.1)
Response to immunomodulators			
Response	22 (34.4)	4 (20.0)	18 (40.9)
Remission	22 (34.4)	0 (0.0)	22 (50.0)
Adverse effects from immumomodulators	2 (3.5)	0 (0.0)	2 (5.4)
Biologics after IPAA	31 (22.6)	13 (59.1)	18 (15.7)
Response to biologics			
Response	9 (25.0)	5 (33.3)	4 (19.1)
Remission	12 (33.3)	0 (0.0)	12 (57.1)
Adverse effects from biologics	0	0	0
Long-term seton placement	25 (18.8)	7 (33.3)	18 (16.1)
History of abscess drainage	38 (28.4)	8 (36.4)	30 (26.8)
Pouch—vaginal fistula	23 (31.5)	4 (40.0)	19 (30.2)
Endoscopy balloon dilation of pouch stricture	24 (17.9)	4 (18.2)	20 (17.9)
Pouch-related hospitalization			
For medical treatment	19 (13.9)	2 (9.1)	17 (14.8)
Nonresection surgery	7 (5.1)	0 (0.0)	7 (6.1)
Post-IPAA pouch-related hospitalization	43 (31.4)	19 (86.4)	24 (20.9)
Extraintestinal Manifestations	66 (48.2)	13 (59.1)	53 (46.1)

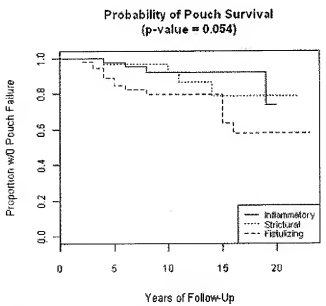

FIGURE 1. Comparison of pouch survival with different phenotypes of Crohn's disease of the pouch.

have IPAA. That was why only 4 patients with a preoperative diagnosis of Crohn's colitis underwent restorative proctocolectomy in this series. De novo CD of the pouch was by far the most common.

The etiology, pathogenesis, and natural history of CD of the pouch are not clear. CD of the pouch is one of the leading causes of pouch failure resulting in pouch resection or permanent diversion. It is not clear whether the subset of patients with IPAA developed CD because of possible missed subtle changes in CD during preoperative or intraoperative evaluation or because of an altered bowel anatomy creating a "CD-friendly" environment. Although small bowel ulcers, nonanastomotic ulcerated strictures, fistular formation, and in some cases, the presence of granulomas on histology are indicative of CD, it is also possible CD of the pouch may represent a unique form of the disease condition of ileal pouch reservoir mimicking CD. We speculate that an altered bowel anatomy with changes in the luminal environment in the pouch reservoir may reset the "thermostat" for the balance and interaction between the genetic, luminal, and mucosal factors in patients with underlying IBD. Further investigation is warranted to elucidate its natural history and pathogenesis. As a matter of fact, CD of the pouch may serve as a human model to study the interaction between genetic, microbiological, and immunologic factors in IBD.

Since the establishment of the Pouchitis Clinic in 2002, we have encountered an increasing number of patients with CD of the pouch, comprising 23% of the patient population. This unusually high percentage should not reflect the true prevalence of CD among the patients with IPAA in general practice. The main goal for the establishment of the Pouchitis Clinic was to deliver multidisciplinary care to patients with complex disorders of the ileal pouch, including CD of the pouch. Gastroenterologists or IBD specialists can play a vital role in diagnosing and managing patients with CD of the pouch, with the ultimate goal of saving the pouch. Conservative treatment modalities include pharmacotherapy[28] and endoscopic balloon dilation of strictures.[29] Biologics such as infliximab appeared to be effective in short-term induction of fistulizing CD of the pouch.[28] Surgical options include strictoplasty,[30] incision and drainage, seton placement, and conversion of a J pouch to a continent ileostomy. However, the management of CD of the pouch is often challenging, and its prognosis is yet to be improved. In the current study, 22 patients (16%) developed pouch failure, with a median follow-up of 2 years after the diagnosis of CD at the Pouchitis Clinic was made, despite medical (including use of immunomodulators and biologics), endoscopic, and pouch-sparing surgical therapies.

Our recent study showed that a diagnosis of the CD of the pouch was associated with a 7-fold increase in risk of pouch failure.[31] The identification of risk factors for pouch failure in patients with CD of the pouch has not been previously investigated, largely because of a relatively small number of patients scattered in private and academic practices.[15,32,33] Taking advantage of the established Pouchitis Clinic, we were able to enroll 137 patients, 22 of whom developed pouch failure, which allowed us to conduct meaningful statistical analyses. In the current study, we found that younger age, being an ex-smoker, and required immunomodulator therapy or biologics was associated with an increased risk of pouch failure. The results were achieved by using stepwise multivariable analyses. In the univariable analysis, there was a tendency for fistulizing CD of the pouch to possibly be associated with a higher risk of pouch failure. These findings suggest that patients at risk of pouch failure may require close monitoring for symptoms, signs, and response pattern to medical/endoscopic therapy. Frequent endoscopic and radiographic monitoring of disease activity should be carried out for high-risk patients. Special attention should be paid to patients with CD of the pouch who require immunomodulator or biological therapy. However, it is not clear whether medical (with immunomodulators and/or biologics) or surgical intervention may alter the natural course of CD of the pouch, thus reducing the risk of pouch failure.

One of approaches to potentially decrease the risk of pouch failure in patients with IPAA is to identify risk factors for CD of the pouch, hoping that modification of some factors may reduce occurrence of the disease. Reported risk factors for CD of the pouch include preoperative diagnosis of IC,[14] female sex (in a pediatric population),[34] active smoking,[13] longer duration of having a pouch,[13] presence of anti-*sac-*

TABLE 2. Unadjusted Associations: Univariable Cox Proportional Hazards Analysis For Pouch Failure

Factor	Hazard ratio (95% CI)	*P* value
Age (5-year increase)	0.58 (0.46, 0.74)	< 0.001
Duration of UC (5-year increase)	0.39 (0.24, 0.63)	< 0.001
Duration of follow-up (5-year increase)	0.48 (0.12, 1.9)	0.3
Sex (male versus female)	1.5 (0.66, 3.6)	0.32
Smoking (ex-smoker versus never)	1.4 (0.54, 3.7)	0.48
Smoking (current versus never)	1.6 (0.44, 5.5)	0.49
Phenotype (fibrostenotic versus inflammatory)	1.3 (0.32, 5.1)	0.74
Phenotype (fistulizing versus fibrostenotic and inflammatory)	2.8 (1.2, 6.6)	0.023
Configuration of pouch (J versus oOthers)	1.7 (0.39, 7.3)	0.48
Toxic megacolon (yes versus no)	2.3 (0.53, 10.1)	0.27
Precolectomy biological therapy (yes versus no)	1.3 (0.17, 9.8)	0.79
Post-IPAA topical 5-ASA (yes versus no)	2.5 (1.03, 6.1)	0.043
Post-IPAA oral 5-ASA (no versus yes)	1.09 (0.47, 2.5)	0.84
Post-IPAA topical corticosteroids (yes versus no)	4.0 (0.90, 17.4)	0.07
Post-IPAA Oral corticoteroids (no versus yes)	0.31 (0.07, 1.3)	0.11
Post-IPAA long-term Antibiotics (yes versus no)	2.9 (0.67, 12.5)	0.15
Post-IPAA immunomodulators (yes versus no)	5.4 (2.0, 14.9)	< 0.001
Post-IPAA biological therapy (yes versus no)	7.8 (3.3, 18.5)	< 0.001
Long-term seton placement (yes versus no)	2.3 (0.93, 5.8)	0.072
History of post-IPAA abscess drainage (yes versus no)	1.5 (0.65, 3.7)	0.33
Pouch-vaginal fistula (yes versus no)	1.4 (0.39, 4.9)	0.62
History of endoscopic dilations of strictures (no versus yes)	1.2 (0.41, 3.6)	0.73
Hospitalization (yes versus no)	19.7 (5.8, 66.8)	< 0.001
Extraintestinal symptoms (yes versus no)	1.5 (0.62, 3.4)	0.38

charomyces cerevesiae,[15] and family history of CD.[15,21] Our recent studies demonstrated that each phenotype of CD of the pouch had specific risk factors. For example, a preoperative diagnosis of IC was associated not only with CD of the pouch in general[13] but also with fistulizing CD in particular. A younger age and female sex were associated with an increased risk of fistulizing CD of the pouch. The presence of a family history of CD in a patient with underlying UC or IC together with other risk factors such as a younger age may influence the decision about whether to perform IPAA. The patient should be encouraged not to smoke.

TABLE 3. Adjusted Associations: Multivariable Cox Proportional Hazards Analysis For Pouch Failure

Factor	HR (95% CI)	*P* value
Fistulizing Crohn's disease of the pouch	1.08 (0.42, 2.8)	0.87
Ex-smoker	15.7 (2.8, 89.0)	0.002
Use of biologics	4.2 (1.5, 11.3)	0.005
Use of immunomodulators	9.9 (1.7, 57.1)	0.01
Age (5-year increase)	0.60 (0.46,0.77)	< 0.001

There were limitations to our study. First, there might have been referral bias because all patients in the current study were seen in the setting of a subspecialty pouchitis clinic at which patients with a spectrum of pouch disorders were diagnosed and managed. The high prevalence of CD of the pouch among all pouch patients did not reflect the true prevalence of the disease. Second, we calculated pouch survival beginning with inception, where patients were first seen in the Pouchitis Clinic and were diagnosed as having CD of the pouch. However, the exact point at which patients developed CD was not known. Third, the number of patients with CD of the pouch who developed pouch failure was small. Therefore, stepwise multivariable analyses were performed. Because of the sample size, not all potential risk factors for pouch failure were included in the model. We expect that this shortcoming can be overcome in the future as an increasing number of patients with CD of the pouch are seen in the Pouchitis Clinic. Finally, there were no established management algorithms for CD of the pouch. There were variations among our IBD specialists and colorectal surgeons in the selection of medical regimens, determination of the duration

of medical therapy, application of endoscopic therapy, choice of surgical modalities, and decision on timing of pouch resection or permanent diversion.

In conclusion, pouch failure was common in patients with CD. Younger patients and the requirement for immunomodulator or biologics had an increased risk of pouch failure. For the patients at risk for pouch failure, close monitoring of disease activity is recommended. Whether aggressive medical and surgical therapy can alter the disease course of CD of the pouch warrants further study.

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